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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,400	09/17/2001	Brian Andrew Hills	4040.000300	9184

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EXAMINER
HAGHIGHATIAN, MINA

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 10/02/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,400	Applicant(s) HILLS ET AL.	
	Examin r Mina Haghighatian	Art Unit 1616	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radhakrishnan et al (4,895,719) in view of Mautone (5,306,483).

Radhakrishnan teaches method and apparatus for administering dehydrated liposomes by inhalation. Disclosed is a liposome-based aerosol system for delivering a drug, at a controlled release rate, via the respiratory tract. Two discoveries are made, first, rapid systemic uptake of drugs from the site of administration in the respiratory tract can be eliminated or greatly reduced by administering the drug in a predominantly liposome-encapsulated form. Secondly, it was found that the rate of release of a water-

soluble drug from a drug/liposome composition delivered to the respiratory tract can be modulated according to the acyl-chain composition of the phospholipids making up liposomes (col. 2, lines 55-68).

Radhakrishnan also teaches that administration of the $ß_2$–agonist metaproteranol sulfate(MPS) in liposomeal form via inhalation reduced initial plasma levels of the drug more than about 8 fold with respect to free drug, and that plasma levels remained substantially constant over a two hour period. Also disclosed is that $ß_2$–adrenoreceptor agonists, when administered in liposome-entrapped form at a therapeutic dose, produce significantly greater bronchodilation, over an extended time period, than is produced by the same amount of $ß_2$-agonist delivered to the respiratory tract in a free drug aerosol form (col. 3, lines 20-47).

Radhakrishnan discloses that the particles formed have a fine particle size, retain the majority of their originally encapsulated material, and are stable. The delivery device is a metered dose spray device designed to release a selected volume of the suspension in aerosolized form (col. 3, line 48 to col. 4, line 15).

Radhakrishnan teaches the effect of liposome lipid components on the rate of drug release in the respiratory tract, the combination of specific phospholipids and that the effect of lipid charge on drug release rates indicates that the addition of a negatively charged lipid, such as phosphatidylglycerol (PG) at a mole ratio of about 10%, produces a slight to moderate increase in efflux half life. Table 1 discloses some properties of phospholipids used in liposomes (col. 5, lines 5 to col. 6, line 68).

The pharmaceutically active agents suitable for the liposome preparations are listed in column 7, which include albuterol sulfate, terbutaline sulfate, atropine methyl nitrate, cromolyn sodium, beclomethasone, dexamethasone etc. The said preparations contain particles optimally less than about 5 microns (col. 8, lines 30-53).

Radhakrishnan does not teach the separate administration of components and lacks specific teachings on the weight ratios for the components.

Mautone teaches a process to prepare lipid crystalline figures in chloro or hydro fluorocarbon propellants or mixtures thereof for the aerosol delivery of therapeutically active substances. The acellular surface film of the lung, the so-called surfactant system, and the various phospholipids are described in columns 1 to 4. Also disclosed is that the vehicle system for the said invention can deliver for example 5 mg each of DPPC:CP, DPPC:PG or DPPC:CP:PG (200:1, 7:1 or 7:0.35:1, w/w, respectively), which when delivered quantitatively covers 100% of the airspace surface in the lungs of normal adults (col. 4, lines 3-33).

Mautone describes the process of preparing lipid crystals in combination with a therapeutically active substance comprising: preparing a mixture one or more lipids of the group of phospholipids known as phosphatidylcholines and one or more spreading agents, in powder form, and said therapeutically active substance and one or more fluorocarbon propellants (col. 5, lines 5-42). The major lipid component is the phospholipid 1,2dipalmitoyl phosphatidylcholin (DPPC) which is the most surface active of the phospholipids. Another minor lipid component that acts as a spreading agent for

the major component can be diacylphosphatidylglycerol (PG) (col. 6, lines 4-68). Aerosolized drug delivery systems and the method of making them are described in examples I-VI. The administration of the aerosolized drug delivery system and the device are explained in columns 10 and 11.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the preparations of Radhakrishnan by adding the component ratios as taught by Mautone, and because Mautone teaches that the liposome preparations can be administered with or without a drug. Also because of the disclosed benefits of the lung surfactants in respiratory disorders and in carrying drugs into the lung. Furthermore, it would be a logical extension of the combined teachings to prepare the formulations as a combined product, such as a pack and to include patient instructions for proper administration and use.

Claims 1-2 and 6-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bystrom (WO9619199).

Bystrom teaches a proliposome powders for inhalation comprising in a single phase discrete particles of a biologically active component together with a lipid or mixture of lipids having a phase transition temperature of below 37 °C. the powder is particularly suitable for administration by inhalation (page 3, lines 16-22).

Potentially useful lipids may be of natural or synthetic lipids. These lipids are such as DPPC, DSPC, DMPC, DMPG, DPPG etc. Lipids of particular interest in the said

formulations are DPPC and/or DMPC. A mixture of DPPC and DMPC containing at least 10% (w/w) DMPC is preferred, for example 10-50% DMPC (page 4, line 16 to page 5, line 12).

Suitable active components include anti-inflammatory and bronchorelaxing drugs, antihistamines, leukotriene synthesis inhibitors, leukotriene antagonists, glucocorticosteroids, $ß_2$–agonists etc. The active component may also be a mixture of pharmaceutically active substances, for example, a mixture of a glucocortico-steroid with a bronchodilator (page 5, line 21 to page 6, line 10).

Where delivery by inhalation is desired, as much as possible of the proliposome powder of the present invention should consist of particles having a diameter of less than 10 microns, for example 0.01 to 10 microns or 0.1 to 5 microns (page 6, lines 27-30).

Bystrom also teaches that the proliposome powder of the present invention is useful for the local or systemic treatment of diseases and may be administered for example via the upper and lower respiratory tract. The proliposome powder for use in therapy, the use of the proliposome powder in the manufacture of a medicament for the treatment of diseases via the respiratory tract, and a method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the said proliposome powder preparation. The proliposome powder preparation may be used in the treatment of inflammatory diseases in the respiratory tract, for example asthma, rhinitis, etc. Administration to the respiratory tract may be

effected using a dry powder inhaler or a pressurized aerosol inhaler (page 9, line 15 to page 10, line 11).

Although Bystrom does not specifically teach a combination product, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the preparations to a combined product because of the disclosed properties of the liposomes and their benefits in treating respiratory disorders and also the advantages of using liposomes as carriers for drug components.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 703-308-6330. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

JOSE' G. DEES
SUPERVISORY PATENT EXAMINER

Mina Haghighatian
September 20, 2002